IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

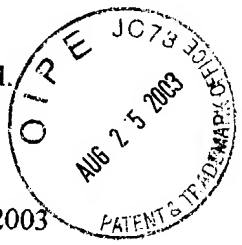
In re Application of:

LAHAV. et al.

Serial No.: 10/018,992

Filed: 19 February 2003

For: STABLE BENZIMIDAZOLE FORMULATION



§ Group Art Unit: 1615

§ Attorney Docket: 24305

Examiner: OH, SIMON J

Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION OF DR. VALERIE AZOULAY UNDER RULE 37 C.F.R. §1.131(a)

I, Dr.Valerie Azoulay, an inventor of the above-identified patent application, declares as follows.

1. Dr. Raffael Lahav, my co-inventor, and I realized the need for a formulation for benzimidazole which would be stable both during storage and during the passage through the stomach. We discussed the fact that many known benzimidazole formulations include an intermediate layer between the core containing the active compound, and the enteric coating layer. Use of such a separating layer involves additional steps during production.

2.We discussed how stabilization could be achieved without use of a separating layer.

3. As a result of our discussions, we conceived of the use of a single neutralized enteric coating layer, having a pH value of at least 6.5, which could be directly coated onto the substrate without any necessity for an intermediate layer. The resultant formulation was

considered to be capable of protecting the product during both storage and during passage through the acidic environment of the stomach.

4. After we conceived of the formulation described above, we commenced tests in our laboratory using preparations of the above formulation.

5. Testing of the formulation in our laboratory involved a large number of *in vitro* and *in vivo* tests to devise and refine the preferred formulation and to carry out dissolution tests, obtain stability data, perform pharmacokinetic and bioavailablity studies, etc. Results of these tests are included in the examples of the present Application. These tests required a considerable input of time, and work was carried out with all reasonable speed.

7. A larger number of experiments were performed regarding neutralization of enteric polymers. Partial and total neutralization was checked for each polymer to select suitable neutralized polymers for the most efficient coating process. The effect of pH on the coating process was investigated in order to obtain a dissolution profile complying with USP specifications for delayed release tablets.

8. A pilot bio-batch was produced, comprising an alkaline tablet core containing Omeprazole, and directly coated with neutralized film former. The test results showed that the formulation for this bio-batch was highly successful.

9. The prior art to Diedrich teaches a "partially" neutralized film former, which is actually two separate layers of an enteric coating having different characteristics, such that one layer is actually an intermediate layer. In a preferred embodiment of the formulation, the film former which is applied to the core is treated with a base to neutralize the free carboxyl groups of the film former, while a dispersion of non-neutralized stomach acid resistant film former or any desired stomach acid resistant coating is also applied until a sufficient thickness is achieved. The neutralized film former taught by Diedrich usually has a pH value of 4 to 8, i.e. in the neutral range.

10. The 'neutralized' film layer taught by Diedrich, which is an intermediate layer (unlike for the formulation of the present invention), has relative basicity with respect to the acidic outer coating layer, which, as is well known in the art, would be expected to lead to interaction between the two layers resulting in degradation of the acid outer coating layer. The result is therefore a non-neutralized outermost layer over a neutralized sub-layer, which is clearly different from the formulation of the present invention.

As a person signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Application or any patent issued thereon.

Dr. Valerie Azoulay

Azoulay
Signature

Date: 27/8/2003